Hyperprolactinaemia – Differential Diagnosis, Investigation and Management

a report by
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DOI:10.17925/EE.2006.00.02.76

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The isolation of human prolactin (PRL) in the 1970s and the recognition that hyperprolactinaemia resulted in a syndrome of amenorrhoea or galactorrhoea was a significant advance.[1] Subsequently, it has been shown that hyperprolactinaemia may be the cause of secondary amenorrhoea in up to one-third of young women. PRL is a 199-amino-acid polypeptide with a molecular weight of 23 kilo Daltons (kDa) that is similar in structure to growth hormone.[1] The main target tissue of PRL has traditionally been thought to be the breast, but PRL receptors have been demonstrated in several tissues, including liver, ovary, testis and prostate.[1] The function of PRL at these sites remains poorly understood.

The predominant hypothalamic factor regulating PRL secretion is dopamine, which inhibits secretion from pituitary lactotrophs.[2] Thyrotropin-releasing hormone (TRH)[3] and vasoactive intestinal peptide (VIP)[4] are stimulatory to PRL secretion, and a further stimulatory factor known as PRL-releasing peptide has also been discovered.[5] However, the physiological importance of these factors is still unclear.

Physiological Elevation of PRL

The most common cause of physiological hyperprolactinaemia is pregnancy,[6] so this must be excluded in all women who present with hyperprolactinaemic amenorrhoea. PRL is stimulated by suckling and remains elevated for a variable period of time during lactation.[7] The extent of the bioactivity of PRL is believed to be important in determining the duration of lactational amenorrhoea.[8] Neural links between the breast/chest wall and hypothalamus are thought to be an important mechanism via which PRL is increased.[9] This mechanism is responsible for hyperprolactinaemia arising from breast stimulation and chest wall and cervical cord lesions. It has been shown that the extent of the PRL rise after breast surgery is of prognostic significance for women with breast cancer.[10] PRL may also be elevated after seizures.[11] Finally, elevations in PRL are part of the human sexual response, with an acute stimulus observed in both sexes following orgasm.[12] It has been suggested that this response contributes to the regulation of sexual arousal and reproductive function.[13]

Pathological Hyperprolactinaemia

The causes of pathological hyperprolactinaemia are listed in *Table 1*. While PRL elevation of virtually any cause can be inhibited by dopamine agonists, it is important to make a more specific diagnosis to optimise management. Clinically, female patients typically present with one or more of secondary amenorrhoea or oligomenorrhoea, galactorrhoea or infertility. Males, on the other hand, often present with symptoms of mass effect, including headache and visual loss, although most have symptoms and signs of secondary hypogonadism on specific enquiry.[14,15] Bone loss leading to osteoporosis may be present; this is a feature of the resulting hypogonadism rather than the hyperprolactinaemia *per se*.[16,17]

PRL-secreting Pituitary Adenomas

Prolactinomas are the most common form of pituitary adenoma, and they make up approximately one-third of all pituitary neoplasms.[18] Pituitary tumours secreting PRL in addition to other hormones are also well described; growth hormone (GH)-secreting tumours may co-secrete PRL,[19] while the combination of adrenocorticotropic hormone (ACTH) and PRL hypersecretion in Cushing's disease is also reported.[20] Prolactinomas, similarly to other pituitary adenomas, are defined in relation to their size on presentation:

- Those that are smaller than 10mm constitute a microadenoma.
- Those that are 10mm or larger constitute a macroadenoma.

The biological behaviour of macroprolactinomas may be inherently different. This is particularly evident in males, where a greater proportion of prolactinomas present as macroadenomas, compared with females, where the majority are microadenomas.[15,21] Males have larger and more invasive tumours, which are more frequently resistant to bromocriptine.[21]

Generally, macroprolactinomas are associated with a more than 10-fold increase in PRL levels to more than approximately 5,000mIU/litre (200µg/litre). A modest elevation of PRL in the order of

Table 1: Major Causes of Pathological Hyperprolactinaemia

Secretory Pituitary Lesions	Non-secretory Hypothalamic–Pituitary Lesions	Other Causes
Prolactinoma	Non-functioning pituitary adenoma	Drugs (see Table 2)
GH/prolactin adenoma	Craniopharyngioma	Renal failure
ACTH/prolactin adenoma	Rathke's cleft cyst	Cirrhosis
	Germ cell tumours	Primary hypothyroidism
	Meningioma	Adrenal insufficiency
	Empty sella syndrome	Polycystic ovary syndrome
	Lymphocytic hypophysitis	'Idiopathic'
	Langerhans cell histiocytosis	
	Sarcoidosis	

1,000–2,000mIU/litre in the presence of a macroadenoma is usually due to a non-functioning pituitary adenoma obstructing the flow of dopamine through the hypothalamic–hypophyseal portal circulation to the normal pituitary lactotrophs.[1] Making this distinction is important, as the majority of prolactinomas will respond to medical therapy with dopamine agonists, while the treatment of choice for a non-functioning pituitary adenoma is trans-sphenoidal surgery. In the case of a cystic lesion, the differential diagnosis must widen to include a craniopharyngioma or Rathke's cleft cyst.[22,23] Sometimes, a definitive diagnosis cannot be made pre-operatively, and if there is compromise to the visual pathways, pituitary surgery may be required. Routine immunohistochemistry on the pituitary tumour surgical specimen can guide the future management of such patients. The presence of positive PRL staining may indicate a dopamine-agonist-responsive tumour.

Non-secretory Hypothalamic–Pituitary Lesions

Among the variety of non-secretory sellar and hypothalamic lesions that obstruct or prevent the flow of dopamine to the lactotrophs and may result in significant hyperprolactinaemia,[24] a non-functioning pituitary adenoma is the most common. However, other neoplastic and inflammatory lesions of the hypothalamus and pituitary and the empty sella syndrome can also cause this, as outlined in *Table 1*.

Drug-induced Hyperprolactinaemia

Significant elevations in PRL may result from a number of commonly used medications (see *Table 2*).[25] As in patients with prolactinoma, this can lead to clinically relevant dysfunction of the reproductive axis in both sexes.[26] In clinical practice, the most common drug classes that result in hyperprolactinaemia are the antipsychotics, anti-emetics and opiates. The diagnosis of drug-induced hyperprolactinaemia requires that structural pituitary lesions are excluded. Where the drug can be ceased or withheld, the demonstration of a normal PRL is usually sufficient to make the diagnosis.[25] There are, however, many patients for whom this is not possible due to their psychiatric condition or chronic pain syndrome. Under such circumstances, performing a magnetic resonance imaging (MRI) scan is advisable.[25]

Table 2: Common Drugs Causing Hyperprolactinaemia

Antipsychotics	Phenothiazines (chlorpromazine and others), butyrophenones (haloperidol), 'atypicals' (risperidone > other atypicals)
Anti-emetics	Metoclopromide, domperidone
Opiates	Morphine, methadone
Antidepressants	Tricyclics, SSRIs, MAOIs
Antihypertensives	Methyldopa, reserpine, verapamil
Oestrogens	
Others	Cimetidine, cocaine, protease inhibitors

MAOIs = monoamine oxidase inhibitors, SSRIs = selective serotonin re-uptake inhibitors.

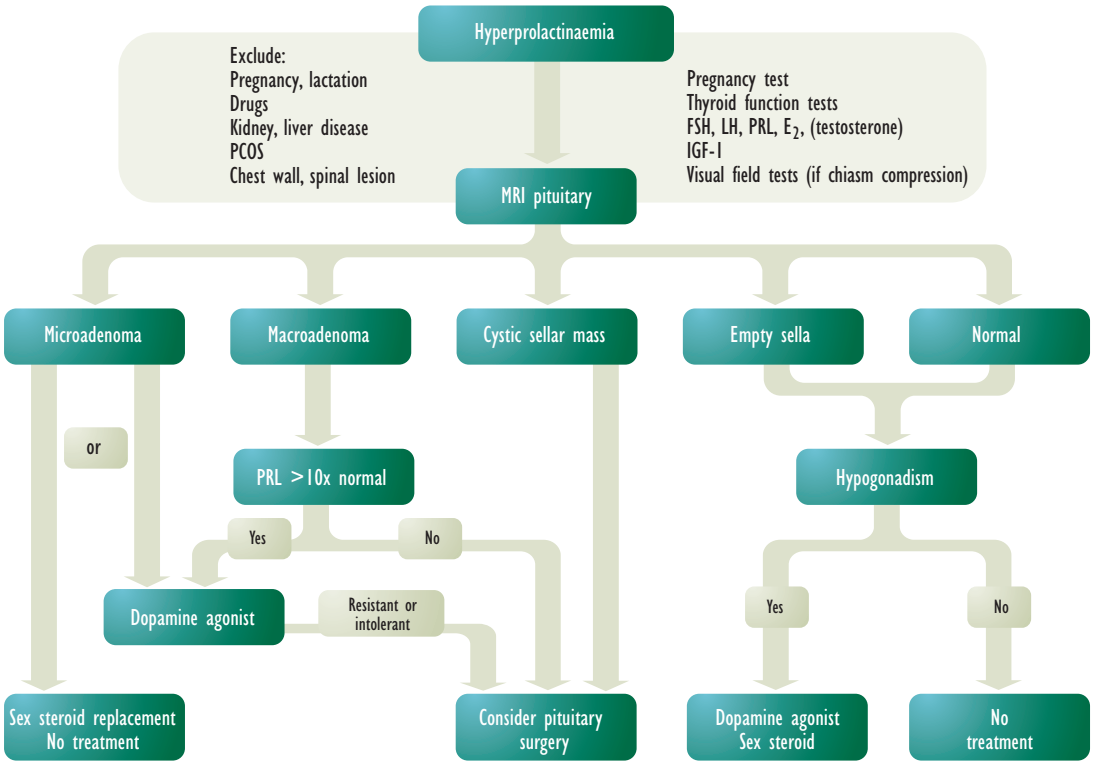
Other Causes of Pathological Hyperprolactinaemia

Hyperprolactinaemia has been noted in patients with renal failure and cirrhosis.[27,28] Primary hypothyroidism can also lead to high PRL levels,[29] mainly due to the stimulatory effect of TRH on PRL secretion.[24] Adrenal insufficiency can be associated with modest hyperprolactinaemia, possibly due to the low cortisol level.[30] Women with polycystic ovary syndrome (PCOS) may have mild hyperprolactinaemia in the absence of a pituitary lesion.[31,32] There remains a small group of patients where no underlying abnormality is discovered; their form of hyperprolactinaemia is termed 'idiopathic'. Follow-up studies of such patients have reassured clinicians that a later discovery of a pituitary adenoma is uncommon, occurring in fewer than 10% of cases.[33,34]

Macroprolactin

In recent years, it has become more widely recognised that some cases of apparent hyperprolactinaemia are not associated with any clinical features despite

Figure 1: Suggested Outline for the Investigation and Management of Hyperprolactinaemia



FSH = follicle-stimulating hormone, LH = luteinising hormone, MRI = magnetic resonance imaging, PCOS = polycystic ovary syndrome, PRL = prolactin.

considerably elevated PRL levels. PRL may form immune complexes with immunoglobulin G (IgG), resulting in a biologically inactive form known as macroprolactin.[35] Macroprolactin may be responsible for elevated PRL in 10% of cases in unselected series.[36] The vast majority of patients do not have any reproductive dysfunction, and pituitary adenomas are present in only approximately 5%.[36] When the macroprolactin is precipitated using polyethylene glycol (PEG), the residual PRL level is normal in most subjects.[37] Different immunoassays may cross-react to a greater or lesser extent with macroprolactin and, in the laboratory, a significant reduction in PRL following PEG precipitation is a useful screen for its presence.[37]

Investigation of Hyperprolactinaemia

A flow chart for the investigation of hyperprolactinaemia is presented in *Figure 1*. The basic principles involve excluding physiological and non-neoplastic causes, pituitary neuroimaging and biochemical assessment of pituitary function. In patients where the hyperprolactinaemia is borderline, measuring it three times at 30-minute intervals using an in-dwelling cannula will exclude any temporary elevation due to stress. Sometimes, using two-site immunoassays, there is marked underestimation of the PRL level due to saturation of both antibodies, the so-called 'hook effect'. Performing the assay using a 1:100 dilution will generally disclose the true PRL level. Where an individual harbours a large sellar mass, it is mandatory to check the remaining anterior pituitary function, particularly to exclude secondary hypothyroidism and hypoadrenalism. It is recommended that insulin-like growth factor 1 (IGF-1) always be measured where a prolactinoma is discovered, as subclinical growth hormone (GH) excess may co-exist. MRI is the radiological investigation of choice. The increased resolution of modern MRI scanners has improved the sensitivity for detecting microadenomas, and the use of gadolinium contrast and dynamic sequences has further enhanced detection. Thus, the number of genuine idiopathic hyperprolactinaemia cases is probably much smaller now than when where CT scanning was relied upon for diagnosis. Visual field assessment may be reserved for patients where there is MRI evidence of impingement on the optic apparatus.

Management of Hyperprolactinaemia

The recognised indications for treating hyperprolactinaemia include hypogonadism (oligo-amenorrhoea in women, androgen deficiency in men), significant symptomatic galactorrhoea and tumour mass effect, particularly where visual pathways are compromised.[24] Where hyperprolactinaemia is asymptomatic, no specific treatment other than periodic observation may be required.[38]

Once a prolactinoma is diagnosed, the usual first line of treatment is with a dopamine agonist.[38] Bromocriptine was developed in the 1970s and there is a wealth of clinical experience, safety and efficacy data regarding it.[39] However, adverse effects limit its use in a significant proportion of cases, despite researchers using it via alternative routes of administration, such as

vaginally and intra-muscularly.[40,41] Currently, the dopamine-2-receptor-specific agonist cabergoline is the most widely used agent in clinical practice. Cabergoline has a longer half-life and greater potency, meaning that a lower dose of drug may be delivered less frequently for a similar or greater effect.[42] A large randomised controlled trial comparing cabergoline with bromocriptine in the treatment of hyperprolactinaemia demonstrated that cabergoline had better efficacy as defined by the return of ovulatory menstrual cycles with fewer side effects.[43] Delivered once or twice weekly, it normalises PRL levels in the vast majority of subjects with pathological hyperprolactinaemia. The usual dose range is from 0.5mg to 3mg per week, but higher doses may be used in resistant cases. Published data regarding macroadenoma shrinkage are uncontrolled, but also demonstrate equal or superior efficacy compared with older studies of bromocriptine, and it occurs in approximately 80% of patients.[44–46] Efficacy is higher in patients who have not previously been treated with other dopamine agonists.[47] Other dopamine agonists that have been used include pergolide and quinagolide.[48,49] Both are effective, but hold no advantages over cabergoline.

The role of pituitary surgery in the management of prolactinomas has been the topic of debate.[50] In most institutions, surgery is reserved for those tumours resistant to dopamine agonists or in which adverse effects have limited their effectiveness. Some centres with considerable expertise have made a case for primary surgery on microprolactinomas.[51] Such an approach allows for a surgical cure, but published recurrence rates tend to be high, and long-term remission may only be achieved in 40–60%.[52–54] Radiotherapy is infrequently used. The rate of decrease in plasma PRL levels is slow and the remission rate low.[55] Stereotactic radiosurgical techniques, such as the gamma knife, may be more effective, but are still regarded as third-line therapy.[56]

The duration of dopamine agonist therapy should be individualised. Patients with large vision-threatening macroadenomas may require life-long therapy. Recent published data indicate that many patients may enter a long-term remission following treatment with cabergoline.[57] Resolution of the adenoma on MRI is predictive of a long-term remission. Normal PRL levels after bromocriptine withdrawal persist in only 20% of patients.[58] Following a normal pregnancy, hyperprolactinaemia may spontaneously remit in approximately 35% of cases, providing the clinician with an opportunity to review the need for re-instituting therapy.[59] For those female patients who require long-term treatment during their reproductive years, the dopamine agonist can often be stopped at the time of natural menopause.[60] If follow-up MRI scans do not show any evidence of tumour enlargement, no further treatment is generally necessary.

Not all microprolactinoma patients require specific therapy to normalise the PRL level. Women not seeking fertility can usually be safely managed with a combined oral contraceptive.[24] The risk of tumour growth in this circumstance is small, but serial MRI scans are advised to screen for this possibility.[38] In patients seeking pregnancy, the use of bromocriptine is advocated due to its long track record and safety profile.[61] However, to date, there has been no published increase in rates of congenital anomalies in pregnancies conceived on cabergoline.[62–64] As the rate of significant tumour growth during pregnancy is less than 2% for microprolactinoma, most such patients will not require any dopamine agonist therapy beyond a positive pregnancy test.[65] In macroprolactinoma patients, the risk of tumour expansion is higher, approximately 25% in a comprehensive review by Molitch.[61] Unless a patient is at high risk of tumour expansion, dopamine agonist therapy is usually stopped and the patient followed closely on clinical grounds. In the author's unit, visual field testing is undertaken once per trimester, but monthly examinations are advised in higher risk patients. There is no value in monitoring serum PRL levels.[66] Symptomatic tumour enlargement generally responds to re-instituting a dopamine agonist, but, occasionally, surgery is required for vision-threatening lesions.[67]

In the setting of drug-induced hyperprolactinaemia, the patient can sometimes be managed using an alternative preparation;[26] for example, olanzapine and quetiapine tend to cause less PRL elevation than risperidone.[68] Dopamine agonists are sometimes used, although there are reports that these agents can precipitate psychosis in predisposed patients.[69–73] In subjects not seeking fertility, sex steroid replacement in the form of oestrogen (or testosterone in males) may be appropriate, particularly for women of pre-menopausal age with amenorrhoea.[26] If the patient is largely asymptomatic, no specific treatment may be necessary.

Summary

Hyperprolactinaemia may result from a variety of causes, the most important of which are neoplastic pituitary lesions. Hyperprolactinaemia not associated with a pituitary lesion can usually be excluded on the basis of a review of the patient's other medical problems, a good drug history and routine laboratory tests. Distinguishing genuine secretory prolactinomas from non-functioning pituitary lesions is crucial, as the initial management differs. Prolactinomas should firstly be treated with a dopamine agonist; some patients can later be withdrawn, depending on response. Pituitary surgery is generally reserved for patients intolerant or resistant to dopamine agonists or where a non-functioning pituitary lesion is thought to be present. ■

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